REMARKS

The current rejections are all under 35 USC 103 and are as follows:

1) rejection of claims 1, 3-5, and 10 - 19 (composition claims) over a combination of WO 88/08708, Conte and US 5,585,375;

2) rejection of claims 1, 3-5, and 20 (composition claims) over Conte, US 5,585,375 and Nordberg;

3) rejection of claims 39 and 40 (method of treatment claims) over a combination of WO 88/08708, Faber and US 5,585,375; and

4) rejection of claims 24 and 29 -42 (method of treatment claims) over a combination of WO 88/08708, Conte, US 5,585,375 and Riemann.

In view of the repeated use of many of these references, their content and significance will be discussed first before addressing the specific combinations set out by the examiner.

WO 88/08708 (published 1988) describes the use of analogs of galanthamine and lycoramine for treatment of Alzheimer's disease. In the paragraph at page 25 lines 4 - 25, especially at the end of the paragraph it is stated as follows:

> The compounds of the invention may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100-600 mg per day. In preparing such tablets or capsules, standard tablet or capsule-making techniques may be employed. The dosage rate of the compound of the invention or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing tablets. Capsules may be prepared using soft gelatine as the encapsulating agent. If desired, such capsules may be in

the form of sustained release capsules wherein the main capsule contains microcapsules of active compound which release the contents over a period of several hours thereby maintaining a constant level of active compound in the patient's blood stream.

This therefore teaches away from it in placing emphasis on constant levels of active compound in the blood stream. This is precisely what the present invention aims to avoid.

Conte (published 1993) noted on page 7 of the present application describes press-coated tablets for time-programmed release of drugs. The emphasis in the paper is in release of drugs at the proper rate. (See the opening paragraph). The next paragraph points to the desire to produce such compositions comprising antiasthmatic, antihistaminic, psychotropic, anaesthetic, cardiovascular active drugs NSAIDs etc. to make sure that the drugs are administered at the right time. It is noted in the paragraph bridging the columns on page 1017 that compositions of this type may be used to treat night symptomatic recrudescence if administered before sleep. That is that such formulations are designed to result in drug activity during the night. Such compositions delay any release until a shell on the dosage form swells or is eroded away.

US 5,585,375 (published 1996), which is discussed on page 1 of the present application, notes that acetyl choline levels in brain are higgher when animals are awake than when they are asleep and describes use of galanthamine to assist in overcoming jet lag by inhibiting the action of acetylcholinesterase at times when one wishes to be awake, thereby increasing acetyl choline levels at such times.

Nordberg (published 1998) describes the properties of a number of cholinesterase inhibitors used or under testing for use in treatment of Alzheimer's disease. Rivastimine is one that is in use and galanthamine is one under testing. I it is noted that both are in a group of such inhibitors having an elimination half life in the range 0.3 to 12 hours.

Faber (published January 1999) describes the use of propantheline to alleviate the peripheral effects of tacrine (an acetylcholinesterase inhibitor) in use for treatment of Alzheimer's disease.

Rieman published 1994), which is acknowledged on page 6 of the present application, reports on the influence of galanthamine hydrobromide on REM sleep regulation in healthy volunteers and reports that10 and 15 mg doses of galanthamine shortened REM latency, increased REM density and reduced slow wave sleep mainly in the first non-REM cycle.

The present application claims priority from Serial No 60/109611 filed on November 23, 1998. The Faber citation is therefore not a valid reference against this application.

We now turn to the specific combinations of references adopted by the examiner.

As pointed out above, WO 88/08708 in fact points away from the present invention, both as claimed in composition and method of treatment claims in that it teaches that one should aim at a constant level of active compound in the patient's blood stream.

The Supreme Court has pointed out that

> [R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR International Co. v. Teleflex, Inc.* 550 U.S. 398 82 USPQ2d 1385 (2007) .

Rejections based on the disclosure of WO 88/08708 would all seem to lack such a rational underpinning because the whole purpose of the present invention is to avoid the maintenance of a constant level of active compound in the blood but rather to have it drop to insignificant levels during periods where the patient is asleep.

The Examiner cannot modify reference if proposed modification would change principle of operation of prior art invention being modified. MPEP 2143.01(VI). This is precisely what would happen if one were to modify the teaching of WO88/08708 so as to produce a composition or method that does not aim to produce a constant level of active compound but one wherein there are periods of negligible activity..

The fact that Conte teaches that it may be desired that for certain drugs it may be desirable to have them act at a particular time and the fact that it was known that acetyl choline levels are higher when a patient is awake than when asleep, does not overcome this fundamental defect in reliance on WO88/08708. This teaches that for treatment of Alzheimer's disease, blood levels of the active compounds should be kept constant. No other use of the compositions of claim 1 has been suggested by the examiner for which other considerations might apply. In fact even now, conventional wisdom is to keep blood levels constant.

The most widely used treatment of Alzheimer's disease, using the most widely prescribed dug donepezil (Aricept) ignores the insight that lies at the core of the present invention: namely that one does not wish to lower acetylcholinesterase activity any more

than occurs naturally while a patient is asleep. None of the art cited appreciates this. Simply because delayed release formulations have been disclosed for use of galanthamine does not mean that dosing in the particular way set out in the present claims is obvious. No one other than the present inventor appreciated the benefits of dosing in this way. Conventional wisdom was that dose levels should be kept constant. The present invention flies directly in contravention of this conventional wisdom. Aricept, the leading treatment of Alzheimer's disease has a half life that means that its level in plasma is essentially constant throughout activity and rest periods.

As discussed in detail in response to a previous action, the most commonly used drug for treatment of Alzheimer's disease continues to be administered in formulations that are active during sleep and at the time of the present invention, the general consensus was that one should not vary the dosage level of Alzheimer's drugs between the day and night. The art affirmatively chose to medicate AD patients during sleep. Fluctuations in the level of acetylcholinesterase inhibition were thought to be responsible for nausea and vomiting, the leading side effects and reason for discontinuing the cholinesterase inhibitors. The good tolerability of drugs that acted throughout the 24 hour period was attributed to their irreversibility or very long half life, and a shorter-acting cholinesterase inhibitor was recently reformulated into a 24 hour patch.

For practical reasons, the art preferred a continuously-acting cholinesterase inhibitor to one which worked only during the day because of a lower incidence of side effects such as nausea and vomiting. In explaining the good tolerability of metrifonate, an irreversible cholinesterase inhibitor, Schmidt and Henig in the enclosed article state, "The incidence of drug-related cholinergic adverse events is related to the rate of change in cholinergic transmission, rather than to the achieved level of cholinesterase inhibition As the greatest rate of change in cholinergic transmission occurs during the transition from baseline to peak enzyme inhibition, it is, therefore, beneficial to maintain inhibition for as long as possible." [1] A drug that is active only during the day of necessity must go from baseline to peak inhibition every morning, which was understood to be a cause of the most common reasons for drug discontinuation, nausea and vomiting.

Metrifonate and donepezil are drugs which produce continuous cholinesterase inhibition and this was thought to account for their tolerability. "Within the class of acetylcholinesterase inhibitors, metrifonate has a favourable tolerability profile that can be explained primarily by its smooth onset of acetylcholinesterase inhibition...In addition, metrifonate's long duration of action ensures that predictable steady-state levels

[1] Schmidt BH, Heinig R, The pharmacological basis for metrifonate's favourable tolerability in the treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 1998; 9(suppl 2):15-19

of cholinesterase inhibition are achieved and maintained without clinically relevant fluctuations in enzyme activity on a day-to-day basis."[2]

A donepezil study concluded

> "Other cholinesterase inhibitors have also shown efficacy in treating symptoms of AD but are often accompanied by significant or intolerable dose-related cholinergic side effects that have limited many patients' ability to continue treatment. [6,9,26,29] The high frequency of side effects may be partially attributed to peripheral inhibition of ChE (cholinesterase) by some agents. However it may also be that the high rate of side effects is related to the high level of AChE (acetylcholinesterase) inhibition necessary for positive cognitive effects and to rapid rates of fluctuation in AChE inhibition produced by these short-acting compounds. In comparison with the relatively short half-lives of some ChE inhibitors, the long half-life of donepezil (~70 hours) provides relative stability in the extent of AChE inhibition over the course of a day, which may also contribute to the relative reduction in cholinergic side effects seen with this drug." [3]

The preference for 24-hour versus daytime treatment of Alzheimer's disease using cholinesterase inhibitors continues to this day. Rivastigmine, a drug with a high incidence of nausea when given orally, has been reformulated into a 24 hour patch. "It provides smooth, continuous drug delivery, and has the potential to maintain rivastigmine concentrations within an optimal therapeutic window while avoiding the peaks and troughs associated with oral drug delivery… In a 24-week study in 1195 AD patients, the rivastigmine 9.5 mg/24 h patch provided similar efficacy to the highest dose range of capsules, with approximately three-times fewer reports of nausea and vomiting…The patch may be the optimal way to treat dementia patients with rivastigmine." [4]

Thus, there is even today no recognition of the inadvisability of inhibiting acetylcholinesterase [AChE] during the night. Although the Examiner supposes that "one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's or other dementia would not be in need of medication while they are sleeping," researchers in the field of cholinesterase inhibitors felt, and feel there was and is a need to administer medication while patients were sleeping. This need is based on the avoidance of fluctuations in levels of cholinesterase inhibition, and it is demonstrated

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[2] Schmidt BH and Heinig R, ibid

[3] Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, et al, A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 1998; 50:136-145

[4] Cummings J, Winblad B, A rivastigmine patch for the treatment of Alzheimer's disease and Parkinson's disease dementia. Expert Rev Neurother 2007; 7:1457-63

for two of the three cholinesterase inhibitors. The third, galantamine, was produced in a daytime-only formulation only after the submission of this patent application.

The examiner makes the following comment on Conte in making this rejection:

> *"Suitable drugs for such time-programmed release include active agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity"*

The following points should be noted:

1. Galantamine is not known to have daily variations in pharmacokinetics.

2.. Alzheimer's disease does not occur at certain times of the day and not at others. The examples given by Conte include asthma occurring in the early morning hours, stomach acidity increasing during the night and blood pressure increasing during the daytime. As will be shown below, Alzheimer's disease has manifestations of low acetylcholine throughout the 24 hour period whose treatment would be beneficial.

3 .Conte discloses a formulation to treat variations in disease severity dependent on physiopathological changes of circadian rhythmicity. The formulation of the present invention is to reverse the physiopathological changes of the rhythm itself. ("the superimposition of a physiological rhythm of cholinergic activity, via a dosage formulation, onto a brain in which the cholinergic system is deteriorating") Conte does not suggest anything like this.

Later in the same ground of rejection, the examiner comments:

At page 4 paragraph 1, lines 2-3:

"chemicals that interfere with cholinesterase mechanisms are known to promote REM sleep over slow wave sleep. Thus acetylcholine levels clearly depend on physiological and/or physiopathological changes of circadian rhythmicity."

And at page 4 paragraph 2, line 1 and following read:

"Accordingly, it would have been prima facie obvious to one of ordinary skill in the art...to formulate ...galanthamine...into compositions providing delayed release...for use in the treatment of Alzheimer's disease"

Thus, the Examiner states that anticholinesterase medications such as galantamine promote REM sleep, that this depends on acetylcholine which depends on changes in

circadian rhythmicity, and concludes it would therefore be obvious to administer galanthamine in a delayed release fashion for Alzheimer's disease.

The time that it would be "prima facie obvious" to have action of the delayed release, based on this combination of prior art information, is during the sleep period. Precisely the opposite from the present invention.

It had been established in the decade prior to the priority date of this application that REM sleep parameters are decreased in Alzheimer patients. AD patients were reported to have very little REM sleep in comparison to normals (Prinz 1982). REM parameters decreased in proportion to the severity of AD (Vitiello, 1984). Both a decrease in AD and a correlation with severity were confirmed by Reynolds et al (1985) and other reports. Earlier, it had been established that REM sleep facilitated the consolidation of memory processes (Tilley 1978). REM (paradoxical sleep) deprivation after shuttle box learning produced severe retention deficits in animals (Smith 1988), and REM was important for information processing in humans as well (Guerrien 1994). Complex task learning in both animals and humans is followed by a period of REM enhancement (Mandai 1989, Smith 1991). Not surprisingly, enhancing REM sleep was a therapeutic goal in the treatment of Alzheimer's disease (Christos, 199). In the Reimann study, galantamine at the 10 mg dose increased REM sleep, but the 15 mg dose did not. Reimann et al commented that "even 'better' effects on REM sleep variables were observed with the lower dose, " confirming the desirability of enhancing REM sleep.

Thus, if the combination of Conte and Davis 5,585,575, make it "prima facie obvious" that galantamine should be formulated into delayed release, that release, in order to enhance the reduced REM and REM's effects on memory, should occur during sleep in the treatment of AD. This is supported by Reimann. Therefore, it is "prima facie obvious" to administer galantamine during sleep.

The examiner also comments at page 4, paragraph 2, line 12

"Further, one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's or other dementia would not be in need of acetylcholinesterase inhibitor medication while they are sleeping because acetylcholine levels are lower than when the patient is awake. In other words, because acetylcholinesterase is an enzyme that "breaks down" acetylcholine, since acetylcholine levels are already low during the night, there would no need to inhibit the breakdown of already low levels of acetylcholine."

REM sleep was long known to be cholinergic (Jasper and Tessier, 1971 Christos, 1993). The cholinergic deficit in AD was believed to underlie the REM reductions. (Bliwise

1989, Christos 1993, Dykierck 1998). Increasing brain ACh with the cholinesterase inhibitors galanthamine and ENA-713 (rivastigmine, Exelon) was known to increase REM parameters (Reimann 1993, Holsboer-Trachtler 1993, Weinstock 1994) The comments in the Office Response are unreferenced suppositions. The writings of Christos and Reimann indicate, to the contrary, that to those in the art, increasing acetylcholine during sleep in order to enhance REM was desirable.

The question of whether drugs for treatment of Alzheimer's disease fall within Conte's definition of psychotropic drugs has been considered before. Conte does not indicate whether or not cholinesterase inhibitors were considered to be psychotropic drugs. Since Conte is not explicit, a reference used by those in the art was consulted, the PDR. The PDR at the time of the application did not classify Alzheimer drugs as psychotherapeutic or psychotropic drugs and does not to this day. If a psychotropic drug is considered to be any drug that acts on the brain, then why would Conte have listed both "psychotropic" and "anesthetic"? Anesthetics act on the brain. It does seem Conte was using a more narrow definition of "psychotropic" than "drugs that act on the brain," and the most conservative conclusion one could make is that Conte's intent was indeterminate. The applicant therefore maintains that this reference does not cover drugs of the type set out in claim 1. This does not, however, really matter because, as noted above, no art has been cited which suggests other uses for the compounds in question and the art makes it clear that for Alzheimer's disease, the one use that is clearly described, the art taught away from use of compositions that avoided release of active compound for any period.

The combination of WO88/08708, Conte and US 5,585,375 cannot therefore make the composition of claim 1 or any claim dependent on it obvious. Claims 10 - 19 are directed to the very compounds that WO88/08708 teaches should be maintained at constant blood levels.

Similar comments apply to the rejection of claims 1, 3-5, and 20 over Conte, US 5,585,375 and Nordberg. Nordberg teaches that rivastigmine is also an acetyl cholinesterase inhibitor used in treatment of Alzheimer's disease. But there is no more reason given in the cited art to "turn off" rivatstigmine during the night than there is to turn off galanthamine, lycoramine or their analogs. It is therefore submitted that none of claims 1, 3-5, and 20 is obvious over the cited combination of references.

One further comment is, however in order: At page 5, paragraph 4, first line the examiner comments:

"Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate rivastigmine as instantly claimed into compositions providing delayed release...for...Alzheimer's disease."

Rivastigmine was not formulated in fact formulated as the examiner alleges it was prima facie obvious to do. The delayed release form of rivastigmine was a patch providing constant release over a 24 hour period (Cummings, 2007, previously provided). Again this is evidence of the non-obviousness of a formulation designed to "turn off" activity at particular times.

We now turn to the method claims. As noted above, the Faber reference was not published until after the priority date of the present application. Use of probanthine to provide anticholinergic effects is described in the third complete paragraph on page 3 of provisional application 60/109611 from which priority is claimed. The rejection of claims 39 and 40 over a combination of references including Faber is therefore improper.

The final issue for consideration is that of whether the combination of WO88/08708, Conte, Riemann and US 5,585,375 makes the method claims obvious.

As noted above, at the time of the present application, the presumption was that one needed to maintain a constant level of acetylcholinesterase activity and not vary it with time. However, even if this had not been the case, Reimann would not have led one to seek to avoid acetylcholinesterase inhibition at during sleep. The Examiner's position is predicated on the assumption that Reimann would discourage the administration of galantamine during sleep. This is not the case. As pointed out previously, in addition to reporting when galanthamine significantly disturbs sleep, Reimann reports when it does not. In response to the previous action, it was pointed out that steady state plasma levels of the highest dose one would use are below those which caused awakenings after a 10 mg immediate release pill. Thus, one could accomplish all the goals of the Alzheimer community at the time, steady state, increase of REM sleep, ease of administration, with one level-releasing 24 hour pill. This is directly contrary to the present invention.

In responding to the comments made in response to the previous action, the examiner raises the question of unexpected results.

In the Response of September, 2008, we reported an unexpected result of the administration of donepezil (Aricept), whose 72 hour half-life leads to activity throughout the day and night. Donepezil, in comparison to galantamine, produced marked counter-regulatory stimulation of CSF acetylcholinesterase. (Figure now published: Davidsson, 2001, previously submitted). Subsequent experiments in rodents indicate that a contributing factor to the unique elevation of

AChE by donepezil in humans is its activity during the night. Galantamine given to rats so that it was active throughout their 24 hour cycle caused acetylcholinesterase elevations as high as animals receiving donepezil (Hernandez 2006, previously submitted). Thus, the failure of galantamine to produce the marked AChE elevations in humans that donepezil did can be attributed at least in part to its lack of activity during the human rest period.

To summarize, the prior art WO88/08708 taught that it was desirable to maintain constant levels of galanthamine, lycoramine or analog acetylcholinesterase inhibitors in blood when treating Alzheimer's disease. Conte taught that for some drugs delay in release could be useful to make sure that the drugs became effective at the right time and were released at the correct rate, US reported that acetyl choline activity was higher during the day than at night so that if one wished to reset a body clock one could use of acetyl cholinesterase inhibitors to avoid reducing acetyl choline levels during the day, and Reimann taught that galanthamine in some does have an influence on REM sleep. However, nothing pointed to there being any purpose in reducing acetyl cholineserase inhibition and so deliberately reducing acetyl choline levels at night for patients suffering from Alzheimer's disease. The tools for effecting the present invention were all in existence. Means for delaying release were taught inter alia by Conte. Knowledge if the typical pattern of acetyl choline levels was acknowledged in US 5,585,375. However, prior to the present invention, no-one thought there would be any benefit in "switching off" the Alzheimer's treatment as night Conventional wisdom was that one did not wish to do this. Flying in the face of such wisdom is inventive. The claims of the present application define tangible forms of such inventivity.

The invention as claimed is therefore not obvious and does comply with the requirements of 35 USC 103.

In view of the foregoing, it is submitted that this application should be allowed and an early action to this end is respectfully solicited.

Respectfully submitted,

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Medical Hypotheses

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Is Alzheimer's Disease Related to a Deficit or Malfunction of Rapid Eye Movement (REM) Sleep?

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Abstract—Current theories of the cause of Alzheimer's disease (AD) do not address the question as to why AD patients initially and gradually lose their short-term memory, followed later by progressive and accelerated loss of other memory, language, motor skills, perception and very short-term memory. We propose that this pattern of memory loss may be a result of a REM sleep deficit or malfunction. This hypothesis is also supported by:
1) Results which show that AD patients have less REM sleep than controls.
2) There is an established close correspondence between learning/memory and REM sleep. REM sleep deprivation is known to result in impairment in learning recent information.
3) AD patients have a degenerated cholinergic system of the brain. The cholinergic system is known to activate/stimulate the REM sleep process.
4) The lesions in AD victims are primarily located in those regions of the brain that are considered to be active during REM sleep.
5) There is a natural mechanism by which the REM sleep in humans is reduced from 8 hours each day at birth to less than 1 hour each day in old age. An acceleration of this process can lead to possible REM deficit at old age. Furthermore, since old people have so little REM sleep they are more vulnerable to a REM sleep deficit.
The REM sleep deficit mechanism may also work in conjunction with other theories of the etiology of AD, in which case, the REM sleep deficit may explain the progression and/or the acceleration of memory loss in AD. If our ideas are correct, it offers hope that the memory loss in AD may be alleviated or reduced by *prolonged* periods of increased REM sleep. REM sleep deficit may also be useful for early diagnosis of AD disease. Our hypothesis can be tested by more detailed studies of the amount of REM sleep in patients with AD, particularly in the early stages of the disease.

Introduction

Alzheimer's disease (1) is a degenerative brain disorder that results in impaired memory and cognitive function. The disease generally has a very gradual onset, is progressive, and mainly affects old people with risk increasing with age. By the age of 85 the cumulative risk (2) of AD is approximately 20%.

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There are numerous theories (3–5) which attempt to explain the underlying cause of AD. These include a genetic mechanism and the amyloid β-protein (6), toxicity (perhaps due to aluminium (7)), infectious agents (8) and a decline in the cholinergic system (9) of the brain. None of these theories seem to address the important issue that AD patients initially and gradually lose their short-term memory (on the time scale of days), followed later by other long-term memory, language, motor skills, perception and very short term memory (on the time scale of minutes). In the first three of the abovementioned theories, the senile plaques (SP) and neurofibrillary tangles (NFT) which are found in the brains of AD patients (1) on autopsy are thought to result from the influence of some agent. The memory loss is assumed to be a direct result of this neuronal loss. The memory loss is assumed to be a direct result of this neuronal loss. This does not offer an explanation of the observed pattern of memory loss in AD. It is also unexplained why the SP and NFT are primarily found (6) in the hippocampus, the amygdala, the cerebral cortex and other regions of the brain which are important for memory processing and cognitive function. Furthermore, the main types of neurons which are destroyed by the disease are those which belong to the cholinergic system (10). This is also unexplained. A further criticism of these theories is that the SP and NFT are not specific to AD but are also found in the brains of other old people (to a lesser extent) and in patients of Down's syndrome (11) and other brain diseases. The increased risk with age is also not explained in these theories. The causal agents are assumed to remain inert for 60–70 years and thereafter somehow initiate their activity with increasing probability.

We suggest that REM sleep deficit or malfunction may explain why AD patients initially suffer short-term memory loss. This may also offer some hope for an explanation of the location of the SP and NFT which are mainly found in those regions of the brain which are also active in dream/REM sleep. The cholinergic neurons which are primarily destroyed in AD are also known to be active during REM sleep (12).

Memory and REM sleep

Dreaming or REM sleep is thought to play an important biological function (13). Adults have 1–2 h of REM sleep each day while infants have about 5–8 h of REM sleep each day. If one is deprived of REM sleep one night there is REM rebound the next night. Almost all mammals have REM sleep. Continued REM sleep deprivation in animals can even lead to death (see below). There must be some evolutionary advantage in REM sleep. The function of REM sleep is unlikely to be psychological given the large amount of REM sleep in infants.

Most researchers now believe that the purpose of REM sleep is to consolidate recent memories and to facilitate the learning process (12). Experiments with animals (14) have shown that increased learning is followed by increases of REM sleep, and that learning is impaired by REM sleep deprivation. Recent experiments have also shown that learning is impaired by REM sleep deprivation in humans (15). The content of dreams primarily consists of recent events and information acquired in the last few days. This was known to Freud (16) and has been established by detailed experiments (17) where subjects wore goggles with red glass. The coloured shading gradually penetrated into the dreams of the subjects and after a few days almost all dreams involved a red shading. When the goggles were removed the red colouration disappeared after a few days. Together these results suggest that dreaming is a process by which the brain reprocesses *recent* information into memory. By the same token this process helps the brain to eliminate or reduce unwanted information that is 'unintentionally' acquired or generated within the brain (so called spurious or parasitic states—see discussion below).

Winson (18) has speculated that in REM sleep the brain is rehearsing those events which are important for survival. Some mammals emit a distinctive brain signal of approximately 6 cycles per second (observed by an electroencephalogram) from the hippocampus region when they are performing an important task (19). This task is different for different animals. It is also known that all of these mammals also emit these so called theta waves during REM sleep. The theta rhythm has not been observed in humans but it can be argued on evolutionary grounds that we may have developed through such a phase and the function of our REM sleep is unlikely to be much different. Crick and Mitchison (13) on the other hand have suggested that REM sleep is a reverse-learning mechanism. Based on Hobson and McCarley's observation (20) that dreams are periodically stimulated by random input generated in the brain-stem, Crick and Mitchison have suggested that during dreaming these random inputs are processed until they reach a final attractor and that final state is partially unlearned from memory. At first sight this may appear to be opposite to the notion that REM sleep and learning are correlated, but this is not the case. Work on artificial neural networks (21) has shown that when patterns are stored within a neural network, the network also generates other states which are combinations

of the stored memories or generated entirely by the network. Although these parasitic memories are quite shallow, they are numerous and affect the storage capacity and the efficiency of the neural network. In the postulated reverse-learning mechanism the partial unlearning of dream attractors removes many of the parasitic states but has little effect on the deep stored memories. The result of this is that the (recent) strong intentional memories are relatively amplified by this process, hence improving learning.

What are the possible side-effects of REM sleep deprivation, deficit or malfunction? The latter may also include (partial) failure of the chemical processes associated with the relearning or unlearning process of dreaming. As noted earlier, learning is impaired by mild REM sleep deprivation in both animals and humans. The effects of prolonged REM sleep deprivation on humans are not known since it is difficult to continue with such experiments after a few days because it is practically impossible to stop the subjects from having REM sleep. In an ingenious experiment (22) in the 1950s Jouvet placed cats on small islands surrounded by water. When the cats fell into REM sleep the resultant relaxation of their muscles caused them to slip off their islands into the water, waking them up. After a few weeks of REM sleep deprivation some of the cats died, while the others showed very strange behaviour.

Alzheimer's disease and REM sleep

If we assume that REM sleep is important for the processing of recently acquired information then a deficit of REM sleep over a substantial period might be expected to result in an overall decline in memory processed during that period. The information acquired since the onset of the REM sleep disorder would be the most affected. We suggest that such a mechanism may be responsible for the short-term memory loss observed initially in AD. In addition a reduction in the amount of REM sleep would result in an increase in the number of parasitic memories. This would in turn progressively make the brain operate less effectively and would eventually affect other memory and cognitive function. The continued decline of the brain by this process may eventually affect language, motor skills, perception and even the ability to process immediate information.

The hypothesis that the memory loss in AD is related to REM sleep deficit is supported by results (23) which show that demented patients (including AD) have less stage 2 and REM sleep than controls. The control groups where found to have almost twice as much REM sleep as the demented patients. The statistics in this study are quite limited and further work, especially with AD patients, would be required to confirm these results and to test our hypothesis. To determine whether the REM sleep deficit is the cause rather than the effect of dementia it would be desirable to perform such studies on patients in the early stages of AD.

The other interesting finding in AD is that the neurons which are mostly affected by the disease are the cholinergic neurons (9, 10). This is particularly interesting since the cholinergic system is known to stimulate REM sleep and its degeneration may cause (or be associated with) REM sleep deficit and subsequent memory loss. Patients of AD show reduced levels (24) of the neurotransmitter acetylcholine (ACh) and the enzyme choline acetyltransferase, which is important for the synthesis of ACh, by as much as 90% in some parts of the brain such as the hippocampus and the nucleus basalis of Meynert. It is also known that certain drugs (such as scopolomine) which interfere with the activity of ACh produce symptoms in controls which resemble AD (25). This led to the hope that the use of drugs which stimulate the production, level or activity of ACh may help to alleviate or reverse AD. Such attempts have had very limited success (26). In other unrelated work, it has been observed that the injection of cholinergic agonist drugs into the pons region of the brain-stem actually induces REM sleep (27). Injection into neighbouring regions, such as the midbrain, produces instead intense arousal (28). The problem with previous treatments may partly lie in the method of administration. One of the other difficulties with a miracle drug is that other neurochemicals (29) are also depleted in AD, especially after a prolonged period of the disease, and their interactions as a whole may then become important. Furthermore, if memory loss in AD is due to long periods of REM deficit then treatment may require sustained periods of drug use.

The hypothesis that a REM sleep disorder causes AD is unable to provide a clearly satisfactory explanation of the SP and NFT. The same criticism can also be levied against the other theories of the cause of AD which are really also unable to explain the actual mechanism by which these neurons die. A possible scenario might be that with age there is an increased likelihood of a potential decline in the REM sleep process or the cholinergic system. It is already known (30) that the amount of REM sleep in humans reduces gradually from 8 h each day for a newborn to just less than 1 h each day in old age. An acceleration of this natural process can lead to possible REM deficit in old age. Furthermore since old people already have so little REM sleep they are more vulnerable to a re-

duction in the amount of REM sleep. The REM sleep dysfunction may then lead to the demise or death of the cholinergic neurons which the brain-stem would normally stimulate, because of their reduced or diminished activity. It is interesting to note that the lesions in AD are found in those parts of the brain that are important for memory and cognitive function which are also active during REM sleep. Alternatively our suggestion that REM sleep deficit may explain the memory loss in AD might work in conjunction with other theories of the cause of AD. The REM sleep idea may explain the progression and/or the acceleration of memory loss in the disease. In this case some agent (such as amyloid β-protein) may have an affinity to the cholinergic system or neurons (or to the neurons in the hippocampus, the amygdala or the nucleus basalis of Meynert) whose demise may result in a REM sleep deficit/malfunction and subsequent memory loss.

Other comments

There is another interesting fact that may connect AD and REM sleep. It is known (31) that injection of melatonin into the brains of rats results in increased REM sleep and that deprivation of REM sleep normally results in elevated levels of melatonin in the pineal gland located in the brain. This increased melatonin level might be produced to stimulate REM rebound. It is interesting to note that AD patients have less REM sleep and reduced levels of melatonin.

Depression is usually associated with an increased pressure for REM sleep. Anti-depressant drugs reduce the amount of REM sleep. In a reported case study (32) a patient, who was later diagnosed with AD, was initially thought to be suffering from depressive illness. The doctor prescribed an anti-depressant drug. To quote: 'If anything, the medicine seemed to make Harry's memory worse'.

Interest in the amyloid β-protein theory (6) and the genetic connection is heightened by the discovery that the precursor to this protein is produced by a gene located on chromosome-21. Down's syndrome (DS) results from an extra copy of chromosome-21 and it is known that DS patients generally develop AD (or its symptoms) after 40 or 50 years of age. The genetic connection for AD can however potentially only account for some of the familial types of AD. In our view this connection may also raise questions about the underlying cause of the diminished cognitive function and impaired learning which is observed in DS. Can DS and mental retardation have something to do with REM sleep malfunction? A REM sleep malfunction would make it more difficult to learn.

Summary

REM rebound suggests that REM sleep serves an important biological function. Furthermore, there is an intimate link between the amount of REM sleep and learning. On the basis of this it is reasonable to believe that a deficit or malfunction of REM sleep would lead to a decline in the consolidation of recent memory. Theoretical ideas and mathematical models suggest that REM sleep is also important to reduce parasitic memory states which are generated within the neural network. A reduction in the amount of REM sleep would then be expected to also render the brain less effective and continued REM sleep deficit would result in a progressive and accelerated decline of other long-term memory, including language, motor skills and perception. We have suggested that AD may result from this scenario. Our hypothesis is supported by results which show that AD patients have about half the amount of REM sleep as controls and that AD patients have a damaged cholinergic system which is important in the stimulation of REM sleep. We have further suggested (in an attempt to explain the NFT and SP) that the REM deficit may lead to neuronal death in the hippocampus, amygdala and the cerebral cortex because of the inactivity of these neurons. Subsequent damage to the hippocampus and the amygdala, as evidenced by research (33) on the famous patient 'H.M.' who had his hippocampus and amygdala bilaterally removed, may then result in the inability of the AD patient to process immediate very short-term memory. This is a characteristic feature of AD patients after a few years of the disease.

As mentioned earlier an analysis of REM sleep in patients in the early stages of AD may determine whether REM deficit is the cause or the effect of dementia. Whether the REM sleep deficit is cause or effect is relatively unimportant if it can help to alleviate or retard the problems associated with memory loss in AD. If our ideas are correct they also offer hope of early clinical diagnosis of AD. Experiments have shown there are very minor or no obvious psychological effects in limited (in the order of a few days) REM sleep deprivation (34). For this reason we expect AD to result from long periods of REM sleep deficit. Consequently we would expect that a prolonged period of increased REM sleep would be essential for any beneficial effect to AD patients.

Acknowledgements

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Physiol Behav. 1989 Oct;46(4):639-42.

REM sleep modifications following a Morse code learning session in humans.

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Various experimental data indicate that rapid eye movement (REM) sleep is involved in learning processes. In animals, any complex task in a learning environment leads to an increase of the consecutive total REM sleep time, especially just before learning completion. In humans, the oculomotor activity during REM sleep seems to constitute an interesting marker of learning performance. In this work, we focus on the qualitative analysis of REM sleep characteristics after a Morse code learning session. Eight male subjects were polygraphically recorded during three consecutive nights. A computer aided teaching session was performed just before bedrest onset of the experimental night. The learning performance (percentage of saving) was checked on awakening. The Morse code learning led to some modifications in REM sleep components, particularly increases of REM sleep time and number of REM episodes. We did not observe any significant modification in the total number of REMs in the experimental night. However, the correlative analysis between learning performance and sleep parameters indicates a superior r for the oculomotor activity than for the tonic components. This is consistent with the information processing hypothesis in which the temporal distribution of REMs reflects the subject's ability to increase the signal-noise ratio from environmental information intake.

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J Am Geriatr Soc. 1982 Feb;30(2):86-93.

Changes in the sleep and waking EEGs of nondemented and demented elderly subjects.

Prinz PN, Peskind ER, Vitaliano PP, Raskind MA, Eisdorfer C, Zemcuznikov N, Gerber CJ.

Sleep and waking EEGs from 11 healthy nondemented elderly men and from ten inpatients for whom the diagnosis was probable senile dementia of Alzheimer's type (SDAT), were monitored in the subjects' typical home or ward environments or in the sleep laboratory, according to their customary sleep schedules. Aged normal subjects (age range, 56-85 years) had less Stage 3 and Stage 4 sleep, less REM sleep, and more wakefulness than normally observed in young adults. Patients with SDAT (age range, 56-88 years) had even less Stage 3 sleep, no Stage 4 sleep, and very little REM sleep, and experienced fragmentation of their sleep, with frequent awakenings. These sleep variables were significantly different in the SDAT and control groups (MANOVA). Examination of the 24-hour plots of sleep/waking patterns revealed prominent fragmentation of the diurnal sleep/waking rhythm in SDAT patients, with frequent daytime napping and nighttime periods of wakefulness. In addition, significant group differences were observed for the EEG variable, dominant occipital frequency. More qualitative EEG variables (diffuse slowing, spindle activity, and paroxysmal discharges) also differed between groups. It is suggested that correlative neuropathologic data might provide an understanding of the basis for the sleep, EEG, and mental-function factors that undergo change in SDAT.

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Biol Psychiatry. 1985 Apr;20(4):431-42.

EEG sleep in elderly depressed, demented, and healthy subjects.

Reynolds CF 3rd, Kupfer DJ, Taska LS, Hoch CC, Spiker DG, Sewitch DE, Zimmer B, Marin RS, Nelson JP, Martin D, et al.

In a prospective study of EEG sleep patterns in 25 elderly depressives, 25 elderly demented patients, and 25 healthy, elderly control subjects, the sleep of depressives was characterized by reduced REM sleep latency, increased REM percent and first REM period density, and altered temporal distribution of REM sleep, as well as by diminished sleep maintenance (correlated significantly with Hamilton ratings of depression: multiple R = -0.42, p less than 0.05). In contrast, the sleep of demented patients showed reduced REM sleep percent, but normal REM temporal distribution, increased loss of spindles and K-complexes (the latter correlating significantly with severity of cognitive impairment as measured by the Folstein score: multiple R = -0.59, p less than 0.01), and less severe sleep maintenance difficulty than for depressives. An examination of REM latency demonstrated a skewed distribution in depression (i.e., 42% of nights with sleep-onset REM periods), but a normal distribution in the controls and demented subjects. A REM latency cut-off score of 30 min correctly classified 68% of all patients (kappa = 0.36; p less than 0.005), compared with 78% correctly identified in our retrospective study (Reynolds et al. 1983).

PMID: 3978175 [PubMed - indexed for MEDLINE]

Biol Psychiatry. 1984 May;19(5):721-34.

Rapid eye movement sleep measures of Alzheimer's-type dementia patients and optimally healthy aged individuals.

Vitiello MV, Bokan JA, Kukull WA, Muniz RL, Smallwood RG, Prinz PN.

It has been suggested that rapid eye movement (REM) sleep measures may be useful in the differential diagnosis of affective disorders. To determine what changes, if any, of REM measures occur in Alzheimer's dementia we examined the REM sleep of nine control and nine mild, nine moderate, and nine severe dementia subjects with probable Alzheimer's disease (AD). Control and mild and moderate AD groups were screened to exclude major depression. REM latency, REM time, REM activity, and REM density were examined. Results indicated that REM sleep measures are minimally affected by mild dementia. None of the REM sleep variables reported here successfully discriminated mild AD subjects from controls. However, REM time and REM latency were significantly affected in later stages of dementia. Total time in REM and REM latency successfully classified control and moderate-severe AD patients. In addition, the pattern of REM density across the night was also affected by severity of dementia. The results of this study, when compared to published REM measure findings in major depression, indicate that with proper cautions REM sleep measures may prove useful in the differential diagnosis of dementia and depression in geriatric patient populations.

PMID: 6733181 [PubMed - indexed for MEDLINE]

Sleep. 1991 Aug;14(4):325-30.

Increases in number of REMS and REM density in humans following an intensive learning period.

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Animal studies have recently demonstrated that increases in rapid eye movement (REM) sleep and actual number of rapid eye movements (REMs) over normal levels followed successful learning of an avoidance task. These increases persisted for many days following the end of the training sessions. It was hypothesized that similar extended increases in REM sleep parameters would follow an intensive learning task in humans. Senior college students were sleep monitored following the end of their Christmas examinations. Results showed that there was a significant increase in the number of REMs observed following the exams as compared to baseline and control subject values. The number of extra REMs was mot prominent during the fifth REM period of the night. A significantly increased REM density was observed at the fourth REM sleep period of the night. Results support the idea of REM sleep and/or the REMs themselves being involved in long-term memory processing several days after the end of training.

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Acta Psychiatr Belg. 1994 Mar-Apr;94(2):75-87.

[Paradoxical sleep and memory processes in humans]

[Article in French]

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The beneficial effect of sleep on memory has often been reported. Moreover, REM sleep seems to be the best candidate for explaining this beneficial effect. Our aim in this paper is to point out the human literature concerning relationships between REM sleep and memory processes. The studies may be separated into three categories, on the basis of their methodological choice: effect of REM sleep deprivation on subsequent performance, effect of learning on subsequent REM sleep characteristics, enhancement of learning by acting on REM sleep. The data strengthen the assumption that REM sleep affects information processing. This topic "REM sleep and memory" is considered with respect to the chronopsychology of memory processes.

PMID: 7502662 [PubMed - indexed for MEDLINE]

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Pharmacological evaluation of phenyl-carbamates as CNS-selective acetylcholinesterase inhibitors.

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The pharmacological and clinical properties of a novel phenyl carbamate acetylcholinesterase (AChE) inhibitor, SDZ ENA 713 are described. In animals and human subjects this compound showed superior chemical stability, oral bioavailability and a longer duration of action than physostigmine. SDZ ENA 713 produced a 10-fold greater inhibition of AChE in the hippocampus and cortex than in the heart and skeletal muscle, which explains its relatively low toxicity and freedom from cholinergic side effects. The selective effect in the cortex and hippocampus may be due to its preferential inhibition of the G1 form of the enzyme, which is present in relatively higher concentrations in these brain areas. Evidence of a selective hippocampal action was obtained in normal human subjects in whom REM sleep density was increased at doses that had no effect on plasma cholinesterase. If memory impairments in AD are related to a lack of cholinergic activity in cortical and hippocampal brain areas, SDZ ENA 713 should produce significant symptomatic improvement.

PMID: 7884403 [PubMed - indexed for MEDLINE]

Display Settings: Abstract

Neuropsychopharmacology. 1993 Jan;8(1):87-92.

Effects of the novel acetylcholinesterase inhibitor SDZ ENA 713 on sleep in man.

Holsboer-Trachsler E, Hatzinger M, Stohler R, Hemmeter U, Gray J, Müller J, Kocher R, Spiegel R.

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A novel brain-selective acetylcholinesterase inhibitor, SDZ ENA 713, is under development for the treatment of dementia of the Alzheimer type. To determine the threshold dose for central activity, single doses of the compound were administered to 20 young male volunteers in a double-blind cross-over design and the effects on the sleep electroencephalography studied. The first group of eight volunteers received in random order: placebo, 0.5 mg; and 1 mg SDZ ENA 713. The second group of 12 volunteers received: placebo, 1.3 mg; and 2 mg SDZ ENA 713. Sleep quality was not affected by the study medication, which was well tolerated by all subjects. A statistically significant increase in rapid-eye movement sleep density was observed after doses of 1 mg, 1.3 mg, and 2 mg. Rapid-eye movement latency and slow-wave sleep were not altered. The results demonstrate that SDZ ENA 713 is centrally active in man at well-tolerated doses.

PMID: 8424849 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

MeSH Terms:

- Adolescent
- Adult
- Carbamates/pharmacology*
- Cholinesterase Inhibitors/pharmacology*
- Double-Blind Method
- Humans
- Male
- Phenylcarbamates*
- Sleep/drug effects*

Sleep, REM/drug effects

Substances:

Carbamates
Cholinesterase Inhibitors
Phenylcarbamates
rivastigmine

Biol Psychiatry. 1989 Feb 1;25(3):320-8.

REM latency in Alzheimer's disease.

Bliwise DL, Tinklenberg J, Yesavage JA, Davies H, Pursley AM, Petta DE, Widrow L, Guilleminault C, Zarcone VP, Dement WC.

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Latency to the first episode of rapid eye movement sleep (REML) has been proposed as a potential biomarker for Alzheimer's disease (AD). In this study, we compared REML values from 28 AD patients and 28 age- and sex-matched controls. We employed multiple definitions of REML and multiple cutoffs to classify patients and controls. Results indicated that the best REML definition and optimal cutoff criterion resulted in only 65% correct classifications. We discuss the longer REML in AD patients relative to controls in terms of both overall sleep disturbance and selective deterioration of the REM-cholinergic system. As REML may be relatively short in other forms of psychopathology (e.g., affective disorders), REML may still hold promise in the differential diagnosis of dementia and pseudodementia.

PMID: 2914155 [PubMed - indexed for MEDLINE]

J Psychiatr Res. 1998 Jan-Feb;32(1):1-9.

The value of REM sleep parameters in differentiating Alzheimer's disease from old-age depression and normal aging.

Dykierek P, Stadtmüller G, Schramm P, Bahro M, van Calker D, Braus DF, Steigleider P, Löw H, Hohagen F, Gattaz WF, Berger M, Riemann D.

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Pseudodementia as a common trait in elderly depressives presents a major problem in gerontopsychiatry, especially for the differential diagnosis between Old-Age Depression (OAD) and Dementia of the Alzheimer Type (DAT). The present polysomnographic study examined parameters of sleep continuity, sleep architecture, and REM sleep to differentiate DAT from OAD. The investigation was based on the theoretical framework of the cholinergic-aminergic imbalance model of depression, the cholinergic deficit hypothesis of Alzheimer's disease and the reciprocal interaction model of Non-REM/REM sleep regulation, according to which REM sleep parameters should have high discriminative value to differentiate OAD and DAT. We investigated 35 DAT patients, 39 OAD patients and 42 healthy controls for two consecutive nights in the sleep laboratory. The DAT patients were in relatively early/mild stages of the disease, the severity of depression in the OAD group was moderate to severe. Depressed patients showed characteristic 'depression-like' EEG sleep alterations, i.e. a lower sleep efficiency, a higher amount of nocturnal awakenings and decreased sleep stage 2. Sleep continuity and architecture in DAT was less disturbed. Nearly all REM sleep measures differentiated significantly between the diagnostic groups. OAD patients showed a shortened REM latency, increased REM density and a high rate of Sleep Onset REM periods (SOREM), whereas in DAT REM density was decreased in comparison to control subjects. REM latency in DAT was not prolonged as expected. To assess the discriminative power of REM sleep variables a series of discriminant analyses were conducted. Overall, 86% of patients were correctly classified, using REM density and REM latency measures. Our findings suggest that REM density as an indicator of phasic activity appears to be more sensitive as a biological marker for the differential diagnosis of OAD and DAT than REM latency. The results support the role of central cholinergic neurotransmission in REM sleep regulation and the pathogenesis of DAT and OAD.

PMID: 9693995 [PubMed - indexed for MEDLINE]

T. J. Teyler and P. Discenna, *Annu. Rev. Neurosci.* **10**, 131 (1987); R. G. M. Morris, S. Davis, S. P. Butcher, *Philos. Trans. R. Soc. London Ser. B* **329**, 187 (1990); B. L. McNaughton and R. G. M. Morris, *Trends Neurosci.* **10**, 408 (1987); P. W. Landfield and S. A. Deadwyler, Eds., *Long-Term Potentiation: From Biophysics to Behavior.* (A. R. Liss, New York, 1987).
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3. Coactivity (simultaneous or near-simultaneous activity)–dependent synaptic change was proposed as a basis for memory by D. O. Hebb [*The Organization of Behavior* (Wiley, New York, 1949)]. Since then, Hebbian synaptic plasticity has been identified in the mammalian central nervous system (*2*), and conditioning studies indicate that responsiveness of single cells can be altered selectively by repeated stimulus pairings [C. D. Woody and J. Engel Jr., *J. Neurophysiol.* **35**, 230 (1972)]. Such changes can be dependent on behavioral state [E. Ahissar *et al.*, *Science* **257**, 1412 (1992)]. This dependence suggests that persistent, rapidly induced changes in functional connectivity between hippocampal cells might be induced through coactivity of these cells during behavior.
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7. In one task, the rat searched steadily within an enclosed box (62 by 62 cm; rats 1 and 3) for a randomly scattered food reward. In the second (spatial working-memory) task, an elongated, X-shaped, four-arm track (167 by 25 cm; rat 2) was used with two adjacent arms designated as start and the opposite two arms designated as goals. The correct goal arm was a function of the randomly selected start arm. Animals were male Fisher 344 rats, approximately 300 g and 9 months of age. All surgical procedures were carried out according to NIH guidelines.
8. Both principal cells (excitatory pyramidal cells) and inhibitory interneurons were recorded during these sessions. Interneurons, identified on the besis of wave shape, firing rate, and spike interval cherecteristics, were not included in the study. Cross-correlations were normalized by spike counts [D. H. Perkel, G. L. Gerstein, G. P. Moore, *Biophys. J.* **7**, 419 (1967); G. L. Gerstein and D. H. Perkel, *Science* **164**, 828 (1969)].
9. Hippocampal EEGs from eight of the unit recording sites were continuously monitored. Sleep phases were predominently characterized by intermittent SPW and ripple activity [J. B. Ranck Jr., *Exp. Neurol.* **41**, 461 (1973); J. O'Keefe and L. Nadel. *The Hippocampus as a Cognitive Map* (Oxford Univ. Press, Oxford, 1978), pp. 150–153; G. Buzsáki, *Brain Res.* **398**, 242 (1986)] with population bursts of variable duration (100- to 300-Hz band EEG, mean duration 74 m, mean inter-burst interval 1.7 s) with little or no REM sleep. The behavioral phase was dominated by thete activity (6- to 9-Hz modulation of EEG and unit discharge), which has been correleted with locomotion [C. H. Vanderwolf, *Electroencephalogr. Clin. Neurophysiol.* **26**, 407 (1969)].
10. Hippocampal neurons exhibit robust selectivity for spatiel location. The preferred location for a given cell is called its "place field" (*J.* O'Keefe and J. Dostrovsky, *Brain Res.* **34**, 171 (1971)]. For each cell pair in which both members exhibited significant spatially related firing in the apparatus, the distance between the locations of their peak firing was used as a measure of overlap (Fig. 1). The criterion for overlap was ε distance between peaks of <16 cm (approximately the diameter of an everage place field). To eliminate any possibility of spurious overlap due to incomplete isolation of single units on a given probe, cell pairs taken from the same probe were eliminated from the analysis. The mean firing rates of cells in coactive cell pairs were the same as those for non-coactive pairs. Thus, the increased correlations were not due to firing rates per se.
11. Figure 2 reveals a tendency for pairs that were negatively correlated (not overlapping) during behavior (see animals 1 and 2 in Fig. 3) to result in reduced correlation during the POST phase. This effect was small end statistically significant only for rat 1.
12. The time constant for decay of correletion was estimated by dividing the initial 10 min of the POST sleep phase into two 5-min periods and computing the mean correlation for overlapping cell pairs in each period. A third point obtained from the mean correlation of the PRE phase was assumed to be the asymptotic base line for the decay. The mean time constant was determined by the fitting of e single exponential to these three points. Rat 1 latency to sleep onset we 20 min, sleep duration was 18 min, and the time constent estimate was 15 min. Rat 2 letency wes 10 min, duration was 20 min, and the time constant wes 9 min. Rat 3 latency was 8 min, duration wes 10 min, and the time constant was 13 min.
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14. For rat 1, cell overlap correletion during ripples was 0.017 ± 0.003 SEM versus 0.005 ± 0.003 ($P < 0.01$) for non-ripples. For rat 2, correlletion wes 0.069 ± 0.008 for ripples and 0.011 ± 0.004 ($P < 0.01$) for non-ripples. For rat 3, appropriate EEG information wes not available.
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Dependence on REM Sleep of Overnight Improvement of a Perceptual Skill

Avi Karni,* David Tanne, Barton S. Rubenstein, Jean J. M. Askenasy, Dov Sagi

Several paradigms of perceptual learning suggest that practice can trigger long-term, experience-dependent changes in the adult visual system of humans. As shown here, performance of a basic visual discrimination task improved after a normal night's sleep. Selective disruption of rapid eye movement (REM) sleep resulted in no performance gain during a comparable sleep interval, although non-REM slow-wave sleep disruption did not affect improvement. On the other hand, deprivation of REM sleep had no detrimental effects on the performance of a similar, but previously learned, task. These results indicate that a process of human memory consolidation, active during sleep, is strongly dependent on REM sleep.

Perceptual learning—the improvement of perceptual skills through practice—is a type of human learning that may serve as a paradigm for the acquisition and retention of procedural knowledge, "habits," or "how to" memories (*1*). Recent results suggest that when observers practice a simple texture discrimination task the large and consistent improvements that occur over the course of several consecutive daily sessions are subserved by discrete changes dependent on retinal input and within an early stage in the stream of visual processing (*2*). Psychophysical data implicate neuronal mechanisms of figure-ground segmentation at a stage in the processing pathway as early as the primary visual cortex in mediating (by becoming more efficient and faster) the learning of this basic visual skill (*2*, *3*). These results, as well as results from several other perceptual learning paradigms (*4*), suggest that different levels of visual processing may, under specific retinal input and task-defined conditions, undergo long-term, experience-dependent changes (functional plasticity) (*5*).

Recently, we and others have found that an improvement in perceptual performance occurs neither during nor immediately after practice but rather 8 to 10 hours after a training session has ended, suggesting a slow, latent process of learning (*6*). As the improved visual skills were not forgotten even

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after an interval of several years, we have proposed that this time course may reflect an active, time-consuming process underlying the consolidation of experience-dependent plasticity within the adult visual cortex. Our study here was designed to investigate the possibility that processes subserving the consolidation of human skills can be supported by mechanisms active during normal sleep. Because normal sleep (unlike the waking state) is parsed into several discrete stages, each with unique neurochemical and electrophysiological characteristics (7), the functional contributions of these brain states to the acquisition of procedural knowledge could be determined.

Six young adults (three females and three males, 17 to 22 years old) with normal or corrected to normal vision and no history of neurological or chronic illness took part in these experiments. Their task was to identify the shape of a small target texture composed of three diagonal line elements that differed only in orientation from a background texture of otherwise identical elements (Fig. 1A). Psychophysical measurements were made both before (initial training session) and after an interval that included either normal sleep or sleep disrupted at a specific sleep stage. An important property of our paradigm, a specificity of the learning for visual field location and background element orientation (2), enabled us to design within-subject comparisons across different sleep conditions, as well as to assess the differential effects of sleep-stage deprivation on performance on a novel stimulus configuration (learning) compared to that on a well-practiced one (control). The latter provided an independent measurement of visual discrimination performance to control for factors such as diurnal variation, stress, and fatigue (8), which would presumably affect performance on a previously learned, as well as on a new, configuration.

The initial night of each study phase was spent at the sleep laboratory with no recording or interference (night 1). This was followed by two consecutive nights of baseline recording during normal sleep (nights 2 and 3) and then by either one or two consecutive nights of deprivation of selected sleep stages when either rapid eye movement (REM) or slow wave (SW) sleep (stages 3 and 4) was systematically disrupted (night 4, or nights 4 and 5 of the study). These in turn were followed by one or two nights of recovery (rebound). Figure 1C depicts the course of one study phase during which REM sleep was disrupted. This was repeated after an interval of at least 1 week (mean = 6 weeks), and the complementary target sleep stage was disrupted. Selective deprivation of selected sleep stages was effected by forced arousal (through the ringing of an electric bell) after an epoch of the relevant sleep stage was recorded. Although this procedure allowed adherence to sleep stage scoring criteria (9), several epochs of the target sleep stage were of necessity included. Sleep stage scoring was done in real time. The recordings were later rescored independently. Two observers completed just one phase of the study (NK, REM sleep deprivation, and IN, SW sleep deprivation).

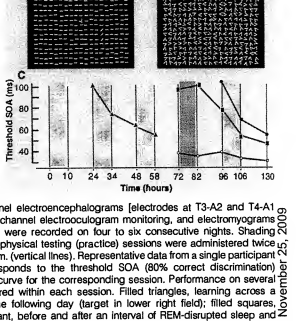

Fig. 1. (**A**) An example test stimulus with a small vertical target texture (three diagonal bars in the right lower quadrant of the display) embedded within a background of horizontal elements. A small rotated letter (either T or L) at the center served as the fixation target. The target texture's position was varied randomly from trial to trial but was always within a specific display quadrant and at 2.5° to 5° eccentricity from the center of the display. (**B**) Mask patterns made of randomly oriented V-shaped micropatterns, with a superimposed T and L micropattern in the center as the fixation letter's mask (*24*). (**C**) The sequence of events within a study phase (pilot study). Standard polysomnographic tracings of two-channel electroencephalograms [electrodes at T3-A2 and T4-A1 (10–20 international system)], three-channel electrooculogram monitoring, and electromyograms (surface electrodes under the chin) were recorded on four to six consecutive nights. Shading represents periods of sleep. Psychophysical testing (practice) sessions were administered twice each day at 9 to 10 p.m. and 7 to 8 a.m. (vertical lines). Representative data from a single participant are shown. Each data point corresponds to the threshold SOA (80% correct discrimination) interpolated from the psychometric curve for the corresponding session. Performance on several stimulus configurations was measured within each session. Filled triangles, learning across a normal night's sleep and during the following day (target in lower right field); filled squares, performance in a new visual quadrant, before and after an interval of REM-disrupted sleep and across the following day and night (target in lower left field); filled circles, performance across an interval of recovery (rebound) sleep (target in upper left field); empty circles, performance on a control, previously well trained, stimulus configuration (target in lower right field, but the orientation of the background elements was flipped to vertical).

Both REM and SW sleep deprivation required 20 to 60 arousals and awakenings, with test participants repeatedly reverting to the disrupted stage (Fig. 2). However, deprivation was quite effective, with REM (a total of seven nights) and SW (a total of six nights) sleep decreasing to 5.7 ± 1.6% (mean ± SD) and 8.1 ± 3.1% of total sleep time (corresponding to 19 ± 6 min in REM sleep and 30 ± 12 min in SW sleep) in the respective deprivation conditions. The difference between time spent in the two target stages during the respective deprivation nights was not significant (*t* test, $P = 0.16$). The mean length of uninterrupted REM or SW sleep was 30 s (a single epoch). Also, the difference between time spent in the awake state in each deprivation condition was not statistically significant (*t* test, $P = 0.27$), and the numbers of arousals and awakenings during the REM and the SW sleep deprivations were comparable (*t* test, $P = 0.34$) (*10*).

Learning, however, was found to be strongly dependent on the type of sleep (Fig. 3). Improvement occurred during normal sleep, with a performance gain of 23 ± 4 ms (mean ± SD) [with thresholds decreasing from 97 ± 18 ms to 74 ± 16 ms (paired *t* test, $P < 0.001$)], but no improvement occurred during a comparable interval with REM-disrupted sleep [performance gain of 0 ± 6 ms (mean ± SD), with thresholds changing from 85 ± 13 ms to 85 ± 18 ms (paired *t* test, $P = 0.42$)] (11). At the same time, performance on a previously learned stimulus configuration was unaffected by REM sleep deprivation. In contrast, significant improvements occurred for all observers after an interval of SW-deprived sleep [performance gain of 19 ± 4 ms (mean ± SD), with thresholds decreasing from 84 ± 13 ms to 66 ± 12 ms (paired *t* test, $P < 0.001$)]. Perceptual learning during the REM sleep deprivation condition compared to the gain during SW sleep deprivation was significantly less [$F(1,12) = 37.009$, $P < 0.001$]. On the other hand, compared to the REM sleep deprivation condition there was a small but significant detrimental effect of SW sleep deprivation on the already learned (control) task [$F(1,12) = 17.896$, $P = 0.001$]. This dissociation suggests that REM deprivation affected the consolidation of the recent perceptual experience, but not perceptual performance by itself, making it

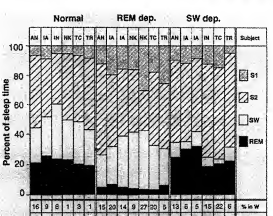

Fig. 2. Percent of total sleep time (TS time) spent in the various sleep stages during normal, REM deprivation, and SW deprivation sleep intervals. The total time in bed (polysomnographic recording time) was 415 ± 29 min (mean ± SD, 38 nights) for the six test participants shown. S1, sleep stage 1; S2, sleep stage 2; SW, sleep stages 3 and 4; % in W, percent of time in bed spent in the awake state; No. of W, number of forced arousals and awakenings during the sleep interval; >5 min, number of episodes of more than 5 min spent in the awake state. No participants had more than 1.5 min in SW stage 4 sleep during the SW deprivation phase. Two participants (IA and NK) underwent two consecutive nights of disruption of specific sleep stages (nights 4 and 5) at one or both experimental phases.

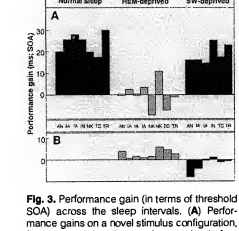

Fig. 3. Performance gain (in terms of threshold SOA) across the sleep intervals. (**A**) Performance gains on a novel stimulus configuration, first presented on the evening session before the sleep interval. (**B**) Performance on a previously well-practiced stimulus configuration (control task). Participant IA was tested during the first night of the REM deprivation phase on two novel stimulus configurations (that is, two independent measurements).

less likely that the effects we observed were nonspecific consequences of disturbed sleep.

Though it has long been hypothesized that memory-related processing, specifically the consolidation of long-term memory, may occur during REM sleep, early experiments designed to demonstrate this for human learning have provided equivocal results. Supporting evidence has come mainly from the work of Empson and colleagues (*12*). Others, however, have found no beneficial mnemonic effects related to REM sleep (*13*) [for recent reviews, see (*14*, *15*)]. One reason for these conflicting results may have been the choice of learning paradigm. Previous studies were concerned with the effects of different sleep stages on the retention of material memorized before sleep (that is, the differential effects of selectively disrupted sleep on the rate of forgetting). Here, we examined how the evolving, time-dependent learning (that is, improvement, not loss) of a simple skill proceeds across both normal and deprived sleep. Thus, two factors may be critical for our results: (i) the fact that a nondeclarative memory system was probed [though it has been suggested that REM sleep may be important for the post-sleep recall of semantically well-integrated materials (*12*, *14*, *15*)] and (ii) the time course of perceptual learning—the finding that people perform much better on a later session than during, or even up to several hours after, the initial one—have provided a more direct measure of the consolidation process.

Our findings suggest that a mnemonic process occurs during normal sleep in the adult brain and that this process is critically dependent on the integrity of REM sleep (*16*). These results are consistent with several paradigms of animal learning in which post-learning REM sleep deprivation has impaired the acquisition and long-term retention of both perceptual and motor "habits" (*14*, *17*). Two lines of evidence converge to suggest constraints on possible neuronal substrates that may underlie the learning of perceptual skills during sleep. (i) REM sleep has been shown to be strongly related to cholinergic activity (*18*). Cholinergic stimulation of the brainstem can elicit a state that is behaviorally and polygraphically indistinguishable from physiological REM sleep. Furthermore, desynchronized electroencephalogram activity (REM sleep as well as the waking state) is correlated with increased amounts of acetylcholine (ACh) in the neocortex, whereas REM deprivation is related to a reduction in the amount of ACh (*19*). (ii) Recent studies have demonstrated that a cholinergic input is a necessary requirement for the evolution of experience-dependent plasticity within the adult sensory cortex (*20*). Thus, a strong cholinergic input may be a critical factor for processes underlying the consolidation of some types of memory. As texture discrimination learning is determined by the specific retinal input presented during the pre-sleep practice session, the role of REM sleep may reside in providing a critical milieu (*21*) for the transformation of the activity-dependent neural change, presumably initiated during the pre-sleep session, into a more efficient and stable (consolidated) modification. A possible mechanism for such a process at the cellular level, suggested by Bear and Singer (*22*), may be for example the ACh-dependent phosphorylation of proteins involved in the long-term, structural modification of synaptic transmission.

We have previously shown that consolidation occurs during the waking state (*6*). Though parsimony would suggest a common process at the cellular level, the question whether the mnemonic process of REM sleep is qualitatively different from the waking state consolidation process remains open. Also open for empirical determination is the intriguing suggestion, raised by Smith and Butler, of specific, spaced REM "windows" occurring after the training session, when consolidation processes are presumably active (*23*). Finally, assuming that a limited repertoire of neuronal mechanisms underlies memory consolidation throughout the mammalian cortex, we conjecture that our results may be generalized to other types of human skill learning (for example, motor skill learning) and perhaps to the formation of some types of long-term association memory.

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11. NK, the only test participant to show some improvement across the REM deprivation interval (on his second deprivation night), had spent more than 5 hours of the interval in the awake state and more than 25% of his total sleep time in stage 1 sleep (see Figs. 2 and 3). Thus, the improvement may have resulted from the waking state consolidation process.
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25. We thank R. Desimone, P. DeWeerd, P. Jezzard, M. Mishkin, J. I. Nelson, and J. Winson for discussions and helpful comments on this manuscript and D. Offenbach for technical assistance. Supported by the Israeli Center for Psychobiology.

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Neutrophil and B Cell Expansion in Mice that Lack the Murine IL-8 Receptor Homolog

Grace Cacalano, James Lee, Kristine Kikly, Ann M. Ryan, Sharon Pitts-Meek, Bruce Hultgren, William I. Wood, Mark W. Moore*

Interleukin-8 (IL-8) is a proinflammatory cytokine that specifically attracts and activates human neutrophils. A murine gene with a high degree of homology to the two known human IL-8 receptors was cloned and then deleted from the mouse genome by homologous recombination in embryonic stem (ES) cells. These mice, although outwardly healthy, had lymphadenopathy, resulting from an increase in B cells, and splenomegaly, resulting from an increase in metamyelocytes, band, and mature neutrophils. Thus, this receptor may participate in the expansion and development of neutrophils and B cells. This receptor was the major mediator of neutrophil migration to sites of inflammation and may provide a potential therapeutic target in inflammatory disease.

IL-8 is a member of a family of proinflammatory cytokines that are related by a C-X-C motif, where X is any amino acid between two cysteines. IL-8 is a major factor in acute inflammation, being responsible for the activation of neutrophils and their chemotaxis to the site of acute injury (*1, 2*). Neutrophils destroy bacteria by phagocytosis and the release of superoxides and peroxides, providing the first line of defense in fighting infection; the response is rapid and is neither acquired nor antigen specific (*3*). Many cells produce IL-8 in vitro, and it has been implicated in neutrophil migration and, to a lesser extent, T-cell migration, to sites of IL-8 injection (*4*). Neither mouse nor rat IL-8 has been identified (*5*), but antibodies (Ab) to human IL-8 inhibit lung inflammation in rats (*6*), which suggests the presence of a similar molecule in rodents.

Two high-affinity human IL-8 receptors have been cloned and characterized (*7–9*). These receptors share 77% amino acid sequence identity and are members of the superfamily of seven transmembrane domain receptors that are coupled to GTP-binding proteins. We have cloned a murine homolog of the human IL-8 receptor by screening a mouse genomic library at reduced stringency with complementary DNA (cDNA) probes from both human IL-8 receptors (*7, 8*). DNA sequencing shows that the mouse receptor is encoded by a single exon (as are the two human receptors) containing a 350-amino acid open reading frame with 68% and 71% amino acid identity with human IL-8 receptors A and B (*10*). Using several different restriction enzymes and genomic DNA blots hybridized under low-stringency conditions, we found a single cross-hybridizing band (*10*), suggesting that unlike the human genome, the murine genome contains a single gene for the putative IL-8 receptor. We refer to this gene as the murine IL-8 receptor homolog (mIL-8Rh).

To determine the function of this receptor in inflammation, we used homologous recombination in ES cells to generate a mouse strain lacking this gene. We constructed a gene-targeting vector by deleting the single exon containing the open reading frame of the mIL-8Rh and replacing it with the neomycin resistance gene (*neo*). This ensures the complete elimination of the gene after homologous recombination (Fig. 1A). Of 814 individual ES clones screened by genomic blot hybridization, 7

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Display Settings: Abstract

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[Paradoxical sleep and memory processes in humans]

[Article in French]

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Université de Lille III, France.

The beneficial effect of sleep on memory has often been reported. Moreover, REM sleep seems to be the best candidate for explaining this beneficial effect. Our aim in this paper is to point out the human literature concerning relationships between REM sleep and memory processes. The studies may be separated into three categories, on the basis of their methodological choice: effect of REM sleep deprivation on subsequent performance, effect of learning on subsequent REM sleep characteristics, enhancement of learning by acting on REM sleep. The data strengthen the assumption that REM sleep affects information processing. This topic "REM sleep and memory" is considered with respect to the chronopsychology of memory processes.

PMID: 7502662 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms

Publication Types:

- English Abstract
- Review

MeSH Terms:

- Humans
- Learning/physiology
- Memory/physiology*
- Mental Processes/physiology
- Sleep Deprivation
- Sleep, REM*

LinkOut - more resources

Medical:

- Memory - MedlinePlus Health Information

Biol Psychol. 1978 Jun;6(4):293-300.

REM sleep and memory consolidation.

Tilley AJ, Empson JA.

One proposal referring to a specific function of REM sleep has been that it is necessary for, or at least conductive to, the progress of memory consolidation. This hypothesis was tested by comparing the effects on story retention of REM deprivation against an S4 deprived control. It was found that recall accuracy following REM deprivation was significantly poorer than following S4 deprivation. Furthermore, the degree of deterioration in recall accuracy during REM recovery sleep was less than during S4 recovery sleep. These findings were interpreted as evidence for active REM facilitation of memory consolidation. However, alternative explanations based upon proactive influences need to be investigated.

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REVIEW

Sleep, Brain Activation and Cognition

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DUJARDIN, K., A. GUERRIEN AND P. LECONTE. *Sleep, brain activation and cognition*. PHYSIOL BEHAV 47(6) 1271–1278, 1990.—Some data have shown the presence of time-of-day effects in learning processes. We explore here whether the same phenomenon occurs during the night and how it relates to REM sleep. In an initial approach to the question, this paper points out the relationships between: 1) REM sleep and brain activation, and 2) REM sleep and information processing. The data are discussed in terms of a REM sleep implication on information processing and we examine the possibility of modifying this processing by acting on REM sleep.

Cognitive processes Brain activation REM sleep Memory enhancement Information processing

ANIMAL studies have revealed the presence of both critical periods for information processing, and rhythmic variations in the recall of information. But human cognitive psychology until now has not generally been involved in this area of research, as if learning mechanisms in humans and animals were different. We assume that the processes involved in learning are subject to time-of-day effects in humans as well as in animals.

Moreover, a whole body of data has shown that an increase in cerebral activity is part of information processing (12). We can then expect fluctuations in the efficiency of information processing over a 24-hour period, related to fluctuations in brain activation during both wakefulness and sleep.

In a primary approach to these questions, this paper focused on the sleep period and points out the relationships between: 1) sleep (particularly REM sleep) and brain activation, and 2) REM sleep and information processing.

Sleep and Brain Activation

The study of reactivity thresholds is of dual concern: traditionally, this kind of research was conducted to determine the depth of sleep (96), but this approach seems just as relevant for dealing with the question of evaluating variations in the sensitivity of the central nervous system (CNS) during the different periods of sleep, and is particularly suited to the question of distinguishing between slow wave sleep (SWS) and rapid eye movement sleep.

This second point is of particular interest to us. In humans, studies on reactivity thresholds may be grouped into two categories on the basis of the choice of responses:

1) When the response does not require any control from the subject (autonomic or EEG responses), reactivity thresholds do not differ from one sleep stage to another (80, 114, 129, 171).

2) In studies were behavioral responses (motor or respiratory responses) are required, there are significant differences in the reactivity thresholds across sleep stages: the reactivity thresholds are smaller in stage 2 and REM sleep than in stages 3 and 4 (80, 93, 94, 132, 175). There is no significant difference between stage 2 and REM sleep, nor between stage 3 and 4 (130,174). Reactivity in stage 2 and REM sleep thus seems to be more similar to reactivity during waking than to reactivity during stages 3 and 4 (94).

Bonnet (20) showed, however, that it is possible to obtain a behavioral response to an auditory stimulus during stage 2 but not during any other stage of sleep. Data from studies on cats are conflicting: reactivity thresholds are generally higher during REM sleep than during SWS (158,165).

All these data must be qualified, however.

Circadian influences interact with the effects of the sleep stages. Corvalan *et al.* (33) show that the thresholds are highest between 10 p.m. and 8 a.m. For a given night, the thresholds are higher during its second half (132, 169, 175).

The significance of the stimulus is also a determinant: thresholds are smaller for significant stimuli (56, 87, 108, 118, 165).

Other factors such as age, kind of stimulus, etc., are also determinant [see Bonnet for a review (18)].

REM sleep seems to be a heterogenous state as far as reactivity thresholds are concerned. The periods with and without phasic activity must be separated. In cats, Gassel and Pompeiano (57) observed phasic increases in the arousal threshold during the REM periods of REM sleep. In humans, Price and Kremen (130) observed the same phenomenon for behavioral thresholds.

Reactivity thresholds thus seem higher during the phasic periods of REM sleep. The CNS is generally more reactive during REM sleep than during SWS.

Studies on the evoked potentials (EP) confirm this hypothesis of an active state of the CNS during REM sleep. In many studies, EP that are very similar, at least in shape, to those recorded during waking are observed during REM sleep, especially the auditory EP recorded cortically (3, 170, 173). More substantial modifications of the EP are observed during SWS, and particularly in stages 3

and 4 (24, 170, 173).

These differences in cerebral excitability, which are dependent on sleep stage, become evident early in ontogenesis. In newborns, the evoked responses recorded during activated sleep approach those recorded during waking, while the EP recorded during quiet sleep are different from those recorded during the two previous states (74).

Stages of sleep do not, however, have any effect on the auditory EP recorded in the cerebral brainstem (23). Other studies confirm the phasic-tonic heterogeneity of REM sleep: enhancement of the visual EP is observed during the phasic periods of REM sleep (133), while during the REM periods of REM sleep Miyauchi *et al.* (110) observed potentials like those of the lambda waves which are related to saccadic eye movements, and which are recorded during waking.

During REM sleep, brain reactivity and brain excitability thus seem to be higher than during SWS: the reactivity thresholds are lower during REM sleep and a stimulation more readily evokes a cortical response during this stage than during the SWS.

These data therefore support our hypothesis of an active state of the CNS during REM sleep. It is indeed possible that the high reactivity of the CNS during REM sleep and the lack of slowing of information conduction, as during SWS, make REM sleep favourable to information processing. Nevertheless, the tonic and phasic activity periods of REM sleep must be distinguished. Data in this area are very dispersed and inconsistent, as we shall see below.

1) Reactivity thresholds are higher during the phasic periods. However, the few studies that have addressed this problem use auditory stimulations. We might therefore wonder whether this phasic increase in the threshold is associated with a problem at the peripheral input level. Baust *et al.* (9) indeed observed muscular contractions in the middle ear during the bursts of REM. This may involve blockage at the auditory stimulation input level, and could thus explain threshold increases. Pessah and Roffwarg (127) observed the same phenomenon in humans.

2) One study showed the enhancement of the visual EP during phasic periods. However, not only was another sensorial modality called upon, but the problem of the peripheral input was avoided by stimulating at the level of the lateral geniculate nucleus (LGN) (133).

The idea that there is marked brain activation during REM sleep is also supported by a series of studies in which the activity of multiple brain formations is recorded during sleep. In the hippocampal cells, the discharge rate is nearly the same during REM sleep as in waking and is slower during SWS (131). The same phenomenon is observed at the level of the midbrain, the cerebral cortex, the thalamus, several limbic formations and the brainstem (100).

During REM sleep, a brain activity pattern that varies with the tonic and phasic activity periods of REM sleep has been found. Lecas (89) showed that brainstem activity is characterized by intensive bursts which are contemporaneous to ponto-geniculo-occipital (PGO) waves, and are superposed on the basal activity. At the hippocampal level, the theta activity of REM sleep is modified when REM burst occurs (31,92). The frequency of the activity peaks of the cortical cells is significantly higher during the phasic periods of REM sleep than during the tonic periods, during which the discharge rate is near to that recorded during SWS (40). The LGN cell discharge rate increases spontaneously during REM sleep. Marks *et al.* (104) showed that in rats, increases in the discharge rate, which are time related to PGO waves, are superimposed this tonic increase of activity.

Additional evidence of this active state of the CNS during REM sleep has been provided by studies showing that a response can be elicited by a stimulus which has acquired the status of conditioned stimulus during the previous waking.

So control by a stimulus of a respiratory response acquired during waking is transferred to sleep whatever the stage of sleep may be, but more readily in stage 2 and REM sleep (7, 25, 68). It has also been shown several times that a sleeping subject can discriminate between a target and a neutral stimulus (118,172). McDonald *et al.* (98) showed, however, that such discrimination is only possible in stage 2 and REM sleep. Other kinds of conditioned responses can also be transferred from waking to sleep: passive avoidance (172) and conditioned salivation (106) in dogs. Several studies show possibilities of habituation for EEG and autonomic responses during sleep, particularly during stage 2 and REM sleep (51,77).

These data have led some authors to wonder whether learning is possible during sleep. The greatest number of studies concerned with hypnopedia have failed to demonstrate the transfer of any learning from sleep to consecutive waking. The retention of material presented during sleep seems possible only when the subject is awake at the moment of the presentation of the material to be acquired or when this presentation induces a pattern of brain activation such as alpha waves on the EEG. In 1956, Simon and Emmons (141) already observed that the retention of any material presented during sleep was possible only when the subject showed arousal cues during the presentation. Many studies have further confirmed these data (22, 48, 78, 79, 84, 115, 140, 155). For a review, see Aarons (1).

Although learning is not possible during sleep, sleep does seem to be involved in memory processes.

Sleep and Cognition

As early as 1924, Jenkins and Dallenbach (76) showed that memory retention is better when the learning session is followed by a sleeping rather than a waking period. More recently, this result was confirmed by several studies (10,75). However, it should be noted that:

1) According to some authors, this beneficial effect of sleeping on retention does not last beyond a limited time (61).

2) There is no consensus about possible differential effects of SWS and REM sleep. Some consider that REM sleep improves memory retention (8,137). For others (45, 55, 174), the beginning of the night, in which stage 4 is considered to be more frequent, plays a leading part. Furthermore, Schoen and Badia (135) failed to show differential effects of SWS and REM sleep.

3) It seems that the beneficial effect of sleep interacts with the circadian rhythms of learning (73).

Other evidence of this effect of sleep on memory can be found in total sleep deprivation studies. When subjects are deprived of sleep during the retention interval, considerable disturbance of memory retention results (4, 9, 150).

As suggested by several studies, REM sleep seems to be the best candidate for explaining this beneficial effect of sleep. With regard to phylogenesis, the parallel evolution of the existence of REM sleep and adaptive capacity could be established in different species: the appearance of REM sleep first in birds agrees with the existence of a long-term memory (42).

From a developmental point of view, the REM sleep rate is highest during the first weeks of life, and gradually decreases down to 30% at age one and to 20% at adulthood (134). Thus, it appears that REM sleep is at its maximum during fundamental acquisition. During the first year of life, one can also observe the evolution of the phasic event structure, and especially an increase in the ratio of REM intervals shorter than 1 second to those longer than 2 seconds ($R = I < 1$ sec/$I > 2$ sec). Petre-Quadens (128) considers this R as an index of cerebral ability to organize

information. Spectral analysis of EEG's shows that the interhemispheric coherence function during REM sleep increases with maturation, and is reduced in cases of prematurity or organic deficit (85,86).

A number of studies also compare REM sleep characteristics with performance on intelligence tests. In mentally retarded subjects, patterns of REM sleep ratios and REM densities below normal have been observed on several occasions (28, 29, 50). The ratio between high and low oculomotor frequencies ($R = 1 < 1$ sec/$1 > 2$ sec) is also a sensitive parameter. Grubar (62) observed a significantly reduced R during nocturnal sleep in mentally retarded subjects. Already in mentally retarded infants, developmental slowness can be observed, which is reflected in the REM sleep patterns of neonates (139). On the other hand, gifted children have a higher REM sleep rate, REM density, and R (63).

As to brain structures, some of them seem to be involved both in memory processes and in the control of REM sleep. Thus, the locus coeruleus (LC), whose importance in initiating and maintaining REM sleep has been shown, is also involved in the control of memory. In rats, Zornetzer and Gold (176) showed that the role of the LC is to delimit the sensitivity period of recently acquired information. Stimulation of the LC leads to substantial enhancement of learning (166). Moreover, Kesner (81) emphasizes the involvement of the hippocampus, both in memory processes and in maintaining REM sleep.

A relationship between sleep structure and environmental factors has also been found. Mice raised in an enriched environment have a higher REM sleep rate than mice raised under standard or impoverished conditions (65). In other studies, exposure to enriched conditions was found to produce an increase in REM sleep and SWS duration, without modification of REM sleep rate (109,154).

In humans, several studies have shown that diurnal activities and environmental factors can modify sleep structure, and particularly REM sleep patterns. In adults, social isolation leads to an increase in REM sleep duration (136,159).

In cases of long-term isolation, this augmentation is followed by a gradual return to the baseline value (153). In addition, REM sleep modifications seem to be related to the novelty of the conditions. In premature babies, a sensorial stimulation schedule applied during waking accelerates the appearance of sleep patterns similar to those of infants born at normal term age, and especially leads to an increase in REM density during activated sleep (11).

Moreover, a number of laboratory studies have investigated the relationships between a controlled learning session and consecutive REM sleep. These studies may be separated into two categories, on the basis of their methodological choice. The first one consists in studying the effects of REM sleep deprivation on memory. The second category investigates the effects of learning on subsequent REM sleep structure. We shall first consider studies on animals, and second studies on humans.

ANIMAL STUDIES

REM Sleep Deprivation Studies

If postlearning REM sleep promotes memory retention, the assumption can be made that postlearning REM sleep deprivation may impair retention. Such a hypothesis seems to have been largely confirmed.

Generally, postlearning REM sleep deprivation is ineffective in simple tasks such as passive avoidance, one-way active avoidance, and simple mazes (70), but impairs memory retention of more complex learnings: shuttle box avoidance (90, 123, 126, 144), complex mazes (39,121), instrumental conditioning (72, 90, 125), discriminative learning (54), latent learning (124), and learning extinction (122).

According to Bloch *et al.* (14), REM sleep deprivation in rats impairs memory when it occurs during the first hour following the learning session. More recently, Smith and his associates (143,145) showed that REM sleep deprivation is disturbing only when it occurs during "windows," which are periods when the appearance of REM sleep is a critical factor for the retention of learning. In mice, Fishbein and Gutwein (52) showed that REM sleep deprivation is disturbing when applied during the 72 hours following learning.

However, some authors have emphasized the methodological problems involved in these experiments. The commonly-used water-tank technique seems to produce several secondary effects: Oniani *et al.* (116,117) showed that when deprived of REM sleep with the water-tank procedure, animals exhibit an increase in spontaneous exploratory behavior and motor activity in the open field. Nonspecific emotional effects like increased stress could also explain the results obtained following REM sleep deprivation (164). The use of other methods that do not produce these nonspecific effects (systematic awakening, pendulum technique, . . .) seems to reduce the disturbing effects of REM sleep deprivation on memory retention (82, 83, 160, 161). Using the water-tank technique, Marti-Nicolovius *et al.* (105) observed facilitation of the acquisition and short-term retention of shuttle box avoidance learning. This facilitation could be the result of the arousal produced by the deprivation procedure. On the other hand, they observed a deficit in long-term retention. For review of these methodological questions, see Hennevin and Leconte (70), Mac Grath and Cohen (101) and Vogel (168).

Learning and Subsequent REM Sleep

Lucero (97) was the first to observe an increase in rats in the REM sleep rate in the first hours following maze learning. This result was largely confirmed by Block and his associates (14, 16, 17, 70, 90, 91) for several tasks: shuttle box avoidance learning, complex maze learning, discriminative learning, extinction of a conditioned response, instrumental learning. Simple tasks such as passive avoidance, however, have no effect on subsequent REM sleep. Moreover, these modifications are observed only when animals have learned: the REM sleep rate does not increase when performance remains poor. REM sleep increases chiefly consist of increases in the number of REM sleep episodes, while the duration of these episodes is not modified. The highest improvement in REM sleep rate is observed in the first hour of sleep; if the onset of sleep is delayed for 3 hours, improvement does not occur.

The existence of distributed learning schedules makes it possible for us to investigate the relationships between various periods of learning and the subsequent REM sleep modifications. It can then be shown that REM sleep increases occur between the first learning sessions and the stabilization of performance, and that the greatest increase is related to the asymptote of the learning curve. At learning completion, the REM sleep rate returns to baseline.

The kinetics of such acquisition and REM sleep modifications may be related to the evolution of other parameters. Maho (102) found that maximum central (cortical arousal) and peripheral (heart and respiratory rates) activation in cats just before the asymptote of the learning curve occurred at the same time as the highest REM sleep increase. Lecas (88) observed the same phenomenon for the reticular and hippocampal levels.

Nonetheless, the characteristics of these REM sleep modifications seem to depend on the task and the animal species. In cats, instrumental conditioning is followed by an increase in the duration of REM sleep episodes during the first 45 minutes of

sleep (88). In mice, REM sleep augmentations following an active avoidance task occur 6 hours after learning, and are maintained for 18 hours (53). Pacteau (119), following an inversion of maze rules task, found a reduction in the latency of modification, although it was longer than in the rat studies.

Destrade *et al.* (38) observed a REM sleep increase after instrumental learning, 3 hours after acquisition. This effect is contemporaneous with the reminiscence phenomenon.

In rats, Smith *et al.* (150) showed that massed active avoidance learning is followed by a REM sleep increase for 6 days, with a latency period below one hour. When the same learning is distributed, the effect occurs only 10 hours after each session. More recently, Smith and Lapp (146,147) observed that post-learning REM sleep augmentations occur during "windows," with a latency varying from 9 to 13 hours and a duration varying from 8 to 11 hours. These windows appear cyclically for 5 days.

These results can be compared to those of REM sleep deprivation studies. Indeed, it seems that deprivations are effective only when they occur at the same time as spontaneous REM sleep increases. Moreover, two kinds of learning can be distinguished: one kind is followed by REM sleep increases, and are impaired by REM sleep deprivation. Such effects cannot be observed with other types of learning. To explain this, the distinction made by Seligman (138) between prepared and nonprepared learning can be considered. The former involve behaviours of the usual repertory, and may be "REM sleep independent"; the latter involve new behaviours, and may be "REM sleep dependent."

HUMAN STUDIES

REM Sleep Deprivation Studies

The effects of REM sleep deprivation in humans also seem to depend on the task. The related studies can be classified into two categories, on the basis of whether or not the REM sleep deprivation impairs retention.

Disturbance effects can be observed in the retention of stories, texts (156), and insignificant sentences (47) in creativity tasks (95) and problem solving (26). On the other hand, REM sleep deprivation is ineffective on the recall of pictures (156) and paired-associates (30, 32, 46, 113), performance on the Q.sort test (27) and serial learning (95).

Lewin and Glaubman (95) proposed distinguishing between two categories of tasks, according to the nature of the involved information processing: tasks requiring structuration of the material and "divergent thinking" seem to be "REM sleep dependent"; tasks with already structured material requiring "convergent thinking" seem to be "REM sleep independent."

Learning and Subsequent REM Sleep

Human studies involve different kinds of tasks and various methodological choices which eliminate the possibility of finding any coherence in the results. These studies can be grouped into the following three categories.

1) Some authors have studied the effect on sleep parameters of several daily activities. In aphasics, Greenberg and Dewan (60) observed an increase in REM sleep during a therapy period. In students, de Koninck *et al.* (34–36) showed REM sleep augmentations during intensive learning of foreign languages. These augmentations were positively correlated with the subjects' performance. However, Meienberg (107) failed to observe such a result. In students during examination periods, Smith and Lapp (148) showed an increase in REM density, without modification of REM sleep duration.

2) Another set of studies concerns the effects on sleep of learning prior to going to bed. In neonates, space orientation conditioning induces a REM sleep increase, without modification of stage 4 (120). In adults, REM sleep parameters are also modified by several kinds of learning. A task involving focal attention was found to be followed by an increase in REM sleep (59). Verschoor and Holdstock (167) investigated the effects on subsequent REM sleep of visual learning as compared to auditive learning. In both cases, the REM sleep rate increased, but an augmentation of REM density was only observed for visual learning.

In our laboratory (103), we recently observed that Morse code learning led to some modifications in REM sleep components: both REM sleep duration and the number of REM sleep episodes increased. However, no significant modification in REM density was observed.

Some studies failed to observe modifications in REM sleep duration, but only showed effects on phasic components. Following acquisition of BASIC calculation rules, Spreux *et al.* (152) observed the intensification of oculomotor activity, without modification of REM sleep rate. In the mental retarded, Gigli *et al.* (58) showed the same effect following an intensive learning program.

When learning is not intensive enough, no modification in postlearning REM sleep components is observed: acquisition of word series (30) or standardized psychometric tests (49) have no effect on subsequent REM sleep.

3) Some authors have studied the effects on sleep of adaptation to visual field distortions. Zimmerman (175) observed an increase in REM sleep rate, while Herrman and Roffwarg (71) showed only effects on oculomotor activity (increase in the amplitude and density of REMs). However, Allen *et al.* (2) and Bowe-Anders *et al.* (21) did not observe these effects. In these studies, the extent of the effects observed seems to be correlated to the degree of distortion.

We may thus consider that intensive learning generally modifies subsequent REM sleep. These modifications can bear on tonic or phasic components, or both. It seems that the nature of the task, its complexity, the required processing, and the involved sensorial modality are determinating factors: different aspects of information processing may have differential effects on REM sleep components.

DISCUSSION

The data we reviewed strengthen the assumption that REM sleep affects information processing: on the one hand, postlearning REM sleep deprivation impairs memory retention, and on the other hand, the postlearning REM sleep structure is modified.

As we have previously shown, REM sleep is characterized by high cortical excitability and reactivity. In the same way, unitary and multiunitary records in several brain structures show a high level of activity. It can thus be concluded that due to the high level of brain activation, REM sleep is a favourable period for information processing. Information processing is indeed known to require a high level of nervous activity. Given that, in 1900 Müller and Pilzecker (112) suggested that the nervous activity induced by perception does not stop immediately, but that this activation persists and is a necessary phenomenon for memory fixation. McGaugh (99) supposed, however, that this fixation is not totally completed immediately after acquisition, but that consolidation is a process which requires time. Bloch (12,13) considers this process to require two stages: some primary processing could take place during the first seconds or minutes following the capture of information; this processing could then be continued during postlearning REM sleep. These two stages may be critical periods during which memory is sensitive to external events. It has indeed been shown that treatments applied at these moments can enhance

or impair memory retention.

a) In the immediate postlearning stage, any treatment impairing brain functions, such as electroconvulsive shocks (44), impairs retention. Moreover, treatments activating the brain functions, such as the stimulation of mesencephalic reticular formation (37), enhance retention. Bloch *et al.* (15) also showed that such treatment prevents the postlearning REM sleep augmentation that normally occurs.

b) For REM sleep, we have shown the impairing effects of postlearning REM sleep deprivation. Several authors have recently investigated the possibility of improving memory by treatments applied during postlearning REM sleep.

The possibility has indeed been shown to intensify and/or prolong the brain activation that normally occurs during REM sleep.

In cats, Drucker-Colin *et al.* (41) showed that auditory stimulations applied at regular intervals at the time of the first PGO wave and for the entire duration of REM sleep induce an augmentation in the amount of REM sleep and in PGO wave density. Arankowsky-Sandoval *et al.* (5) observed similar results by applying the same procedure but using somatic stimulations. Previously, these authors had shown that a reduction in the amount of REM sleep induced by injection of atropine can be eliminated by applying the auditory stimulations. However, atropine injections also induce a reduction in PGO wave density, and stimulation does not have any effect on this phenomenon (6).

In humans, Mouze-Amady *et al.* (111) showed that auditory stimulations applied during the rapid eye movements of REM sleep cause an increase in the REM sleep level related to a reduction in REM density. Investigating the effects on EEG patterns of such stimulation, Sockeel *et al.* (151) observed that this kind of treatment leads to a resynchronization of the brain hemispheres during REM sleep. If such procedures prolong and/or intensify the brain activation that spontaneously occurs during REM sleep, can it not be assumed that they enhance information processing?

We then applied the same stimulation procedure as the one used by Mouze-Amady *et al.* (111) (REM actual auditory stimulations) during the night following a Morse code learning session. This treatment applied during REM sleep led to a significant improvement in the retention of such learning compared to a nonstimulated group. This enhancing effect was no longer observed when the same stimulations were randomly applied during the postlearning night. Moreover, this paradigm (randomly applied stimulations) when applied alone did not induce any modification in the REM sleep parameters (43,64).

In rats, the presentation of contextual cues (that is, the conditioned stimulus of the learning situation) during the REM sleep following an active avoidance learning task leads to both an increase in the REM sleep ratio that is greater than that occurring normally after this kind of acquisition, and an improvement in retention (67,69). The same cues applied during postlearning SWS impair retention (66).

The possibility of interacting with the learning processes during REM sleep supports the assumption that REM sleep is a critical period for information processing, compared to SWS. This is consistent with our assumption that cognition is subject to time-of-day constraints: brain activation seems to fluctuate during sleep, and in relation to REM sleep periods, which seems to condition the efficiency of information processing.

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